Original Paper

Pathogenesis and Pathophysiology of the Cardiometabolic Syndrome

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The cardiometabolic syndrome represents a cluster of metabolic abnormalities that are risk factors for cardiovascular disease. The mechanism(s) responsible for developing the cardiometabolic syndrome is not known, but it is likely that multi-organ insulin resistance, which is a common feature of the cardiometabolic syndrome, is involved. Insulin resistance is an important risk factor for type 2 diabetes and can cause vasoconstriction and renal sodium reabsorption, leading to increased blood pressure. Alterations in adipose tissue fatty acid and adipokine metabolism are involved in the pathogenesis of insulin resistance. Excessive rates of fatty acid release into the bloodstream can impair the ability of insulin to stimulate muscle glucose uptake and suppress hepatic glucose production. Noninfectious systemic inflammation associated with adipocyte and adipose tissue macrophage cytokine production can also cause insulin resistance. In addition, increased free fatty acid delivery to the liver can stimulate hepatic very low-density lipoprotein triglyceride production, leading to dyslipidemia. J Clin Hypertens (Greenwich). *2009;11:761–765.* ©*2009 Wiley Periodicals, Inc.*

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The cardiometabolic syndrome represents a constellation of metabolic abnormalities that are risk factors for cardiovascular disease. The risk of coronary heart disease, myocardial infarction, and stroke is much higher in persons who have the cardiometabolic syndrome than in those without the syndrome.[1] No universally accepted definition of the cardiometabolic syndrome has been established, and at least 5 independent groups have proposed clinical criteria for establishing its diagnosis.[2] The most widely used clinical criteria for diagnosing the cardiometabolic syndrome are those proposed by the World Health Organization[3] and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[4] (Table). The common characteristics of the cardiometabolic syndrome among all groups include abdominal obesity (high body mass index and/or large waist circumference), insulin-resistant glucose metabolism (hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, type 2 diabetes), dyslipidemia (high serum triglyceride and low serum high-density lipoprotein cholesterol concentrations), and increased blood pressure.

PREVALENCE

The cardiometabolic syndrome has become a major public health problem in the United States and many other countries worldwide because of its increasing prevalence. Data from the third National Health and Nutrition Examination Survey (NHANES) (1988–1994) found that the age-adjusted prevalence of the cardiometabolic syndrome, defined by using the ATP III criteria, was 24% in the adult US population.[4] The prevalence of the cardiometabolic syndrome increases linearly

Table. Clinical Identification of the Cardiometabolic Syndrome Based on Criteria From the NCEP ATP III or the WHO

	NCEP ATP III[a]	WHO[b]
Fasting blood glucose	≥100 mg/dL	IFG/IGT/T2DM
Abdominal obesity		
Men	>102 cm WC	>0.90 WHR (or BMI ≥30 kg/m^2)
Women	>88 cm WC	>0.85 WHR (or BMI ≥30 kg/m^2)
Triglycerides	≥150 mg/dL	≥1.7 mmol L^{-1}
HDL Cholesterol		
Men	<40 mg/dL	<0.9 mmol L^{-1}
Women	<50 mg/dL	<1.0 mmol L^{-1}
Blood pressure	≥130/85 mm Hg	≥140/90 mm Hg
Microalbuminuria	–	Yes

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHO, World Health Organization; WHR, waist-to-hip circumference ratio. [a]Three or more criteria. [b]IFG/IGT/T2DM plus ≥2 criteria.

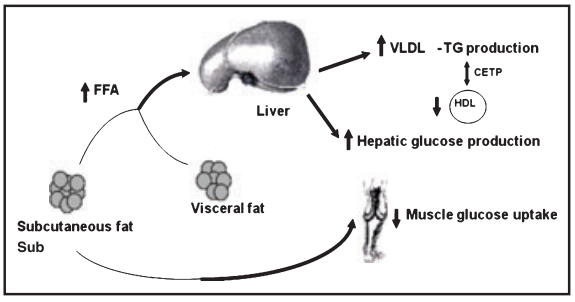

Figure 1. Physiologic interrelationships between fatty acid metabolism, insulin resistance, and features of the cardiometabolic syndrome. CETP indicates cholesterol ester transfer protein; VLDL, very low-density lipoprotein triglyceride; HDL, high-density lipoprotein; TG, triglyceride; FFA, free fatty acid.

with age from approximately 7% in those who are 20 to 29 years old to approximately 45% in those who are 60 years and older. Moreover, the latest NHANES data found that the prevalence of the cardiometabolic syndrome is increasing in both men and women in all age groups.[4]

PATHOPHYSIOLOGY

Fatty Acid Metabolism

The cardiometabolic syndrome is also known as the *insulin resistance syndrome* because it has been hypothesized that insulin resistance is the major mechanism responsible for the metabolic abnormalities of the syndrome.[5] Alterations in free fatty acid metabolism are likely a major factor involved in the pathogenesis of hyperglycemia and dyslipidemia associated with the cardiometabolic syndrome (Figure 1). Excessive release of free fatty acids from adipose tissue into plasma and increased plasma free fatty acid concentration can impair the ability of insulin to stimulate muscle glucose uptake[6] and suppress hepatic glucose production.[7] In addition, increased free fatty acid delivery to the liver can increase hepatic very low-density lipoprotein triglyceride production[8,9] and plasma triglyceride concentration.[10] An increase in plasma triglycerides increases the transfer of triglycerides from very low-density lipoprotein to high-density lipoprotein, which leads to increased high-density lipoprotein clearance and decreased plasma high-density lipoprotein concentration.[11]

Insulin, which inhibits lipolysis, is the major physiologic regulator of basal adipose tissue lipolytic activity.[12,13] Lipolysis of adipose tissue triglycerides is the major source of plasma free fatty acids.[14] Therefore, insulin resistance in adipose tissue stimulates an increase in lipolytic rate and free fatty acid release into the bloodstream. The typical increase in plasma insulin concentrations associated with obesity does not completely compensate for adipose tissue insulin resistance, so insulin-resistant obese persons have high basal lipolytic rates and plasma free fatty acid concentrations.[13]

In skeletal muscle, the cellular mechanism responsible for free fatty acid–induced insulin resistance involves alterations in intracellular insulin signaling and impaired insulin-mediated glucose uptake[15,16] (Figure 2). An acute increase in plasma free fatty acid concentrations from approximately 400 μmol L^{-1} (normal basal concentration) to approximately 800 μmol L^{-1} (concentration during short-term fasting) causes a marked increase in intramyocellular fatty acid metabolites, including long-chain fatty acyl-CoA and diacylglycerol.[15,17,18] These

metabolites are potent allosteric activators of protein kinase C, a serine/threonine kinase that phosphorylates serine/threonine sites of insulin receptor substrate-1, thereby inhibiting insulin's ability to activate phosphoinositide 3-kinase activity[19–21] and decreasing downstream events, including translocation of glucose transporter 4 from the cytoplasm to the cell membrane needed for glucose transport.

Other factors related to intracellular fatty acid metabolism can also contribute to insulin resistance (Figure 2). Defective skeletal muscle mitochondrial function has been identified in persons who have insulin resistance and are at increased risk for type 2 diabetes.[22] Impaired mitochondrial fatty acid oxidation can contribute to impaired insulin action by increasing the intracellular accumulation of fatty acids. In addition, excessive intracellular fatty acids can increase the production of reactive oxygen species, which leads to activation of the proinflammatory nuclear factor kappa B pathway,[17,23] thereby increasing insulin resistance.

The cellular events responsible for fatty acid–induced insulin resistance in the liver have not been as carefully evaluated as in skeletal muscle. Increased delivery of free fatty acids to the liver and possibly increased release of fatty acids from lipolysis of intrahepatic triglycerides stimulate hepatic glucose production.[19–21] Free fatty acid–induced insulin resistance in the liver is associated with activation of protein kinase C.[24]

Abdominal Adipose Tissue

Excess abdominal fat mass, particularly visceral (intraperitoneal) fat, is associated with insulin resistance.[6,7,25,26] However, it is not known whether visceral fat causes or is simply associated with insulin resistance. Visceral fat represents a small component of total body fat mass. Visceral fat accounts for about 10% of total body fat mass in lean men and about 15% of total body fat mass in obese men.[26] Nonetheless, it has been hypothesized that fatty acids released during lipolysis of visceral adipose tissue are an important cause of insulin resistance because these fatty acids enter the portal vein and are delivered directly to the liver.[27] Data from studies that used isotope tracers to assess visceral fat metabolism in vivo in obese persons found that approximately 20% of free fatty acids delivered to the liver and approximately 15% of free fatty acids delivered to skeletal muscle are derived from lipolysis of visceral fat.[28] Therefore, visceral fat might contribute to hepatic insulin resistance, but it is unlikely that visceral fat is responsible for insulin resistance in skeletal muscle.

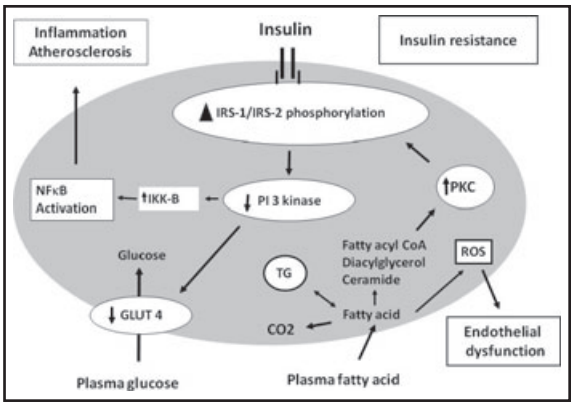

Figure 2. Potential cellular mechanisms for fatty acid–induced insulin resistance. IRS indicates insulin receptor substrate; PI 3 kinase, phosphoinositide 3-kinase; PKC, protein kinase C; TG, triglyceride; ROS, reactive oxygen species; IKK-β, I-kappa B kinase β; NFκB, nuclear factor kappa B. Adapted from Shulman.[16]

Ectopic Fat

Ectopic accumulation of fat in liver and muscle cells is associated with insulin resistance in those tissues.[20,29] Increased intrahepatic fat content is associated with hepatic insulin resistance in the liver and impaired insulin-mediated suppression of hepatic glucose production,[20] and increased intramyocellular fat content is associated with skeletal muscle insulin resistance and impaired insulin-mediated glucose disposal.[29]

Adipose Tissue Secretory Proteins

Adipose tissue produces several inflammatory cytokines (adipokines), which can induce insulin resistance, and adiponectin, which increases insulin sensitivity.[23,30] For example, tumor necrosis factor α suppresses insulin signaling,[31] interleukin-6 increases inflammation directly or by stimulating hepatic C-reactive protein production,[32] macrophage chemoattractant protein 1 is a potent chemoattractant for macrophages,[33] and interleukin-8 activates neutrophil granulocytes and is chemotactic for all known migratory immune cells.[34] Adiponectin increases insulin sensitivity in the liver, decreases hepatic glucose production,[35] and increases skeletal muscle glucose and fatty acid oxidation.[36]

Increased Blood Pressure

The relationship between insulin resistance and hypertension is well established.[37] Fatty acids themselves can cause vasoconstriction.[38] Additionally, insulin resistance can increase blood pressure because insulin is a vasodilator,[39] and hyperinsulinemia increases renal sodium reabsorption.[40] Persons who are insulin-resistant tend to lose the vasodilatory

effect of insulin[41] but preserve the renal effect on sodium reabsorption,[40] and sodium reabsorption is increased in persons with the cardiometabolic syndrome.[42]

CONCLUSIONS

The cardiometabolic syndrome includes a cluster of conditions including abdominal obesity, insulin-resistant glucose metabolism, dyslipidemia, and increased blood pressure. Alterations in fatty acid metabolism (eg, excessive fatty acid release into plasma) likely contribute to these metabolic abnormalities. Increased free fatty acids can (1) impair insulin action in skeletal muscle and liver, leading to increased blood glucose concentration; (2) stimulate hepatic very low-density lipoprotein triglyceride production, leading to increased serum triglyceride and decreased high-density lipoprotein concentrations; and (3) stimulate vasoconstriction and increase sodium reabsorption, possibly leading to increased blood pressure.

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